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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,134	07/23/2003	Redford B. Williams JR.	5405.239CT	8271

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,134	WILLIAMS, REDFORD B.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/05; 11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-16 are pending in the instant application. A first office action on the merits of claims 1-16 follows.

Priority

2. Applicant's claim for benefit of priority from application 60/162,390 is acknowledged. However, the claims have not been awarded the benefit of the filing date of the '390 application because the claimed subject matter is not present in the '390 application. The '390 application is directed to an association between diseases, such as cardiovascular diseases, and presence of the short allele of the serotonin transporter gene promoter. Further, the '390 application does not demonstrate an association between cardiovascular diseases, or any diseases, in response to stress and the long allele of the serotonin transporter gene promoter.

Claim Rejections - 35 USC § 112

Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening human subjects for increased risk of coronary heart disease in response to smoking by detecting the presence of at least one serotonin transporter gene promoter long allele, does not reasonably provide enablement for a method of

screening human subjects for increased risk of disease in general in response to any stress; or broadly any cardiovascular disease, infectious disease, cancer, autoimmune disease, delayed wound healing, or gastrointestinal disease; or for increased risk of infectious disease in general or any specific infectious disease, by detecting the presence of at least at least one serotonin transporter gene promoter long allele, wherein the presence of at least one long allele indicated that said subject is at increased risk of any disease in response to any stress, or any infectious disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Nature of the Invention and the breadth of the claims.

The claims are broadly drawn to screening human subjects for increased risk of disease in response to stress by determining the presence of at least one serotonin transporter gene promoter long allele in a subject wherein the presence of at least one long allele serotonin transporter gene promoter genotype indicates that the subject is at increased risk of any disease in response to

stress. The claims are further drawn to embodiments wherein the disease is cardiovascular disease, cancer, autoimmune disease, delayed wound healing, and gastrointestinal disease. The claims are also broadly drawn to screening human subjects for increased risk of infectious disease wherein the presence of at least one long allele serotonin transporter gene promoter genotype indicates that a subject is at increased risk of infectious disease, wherein the infectious disease can be as claimed in any of claims 7-15. Further, claim 1 does not recite any specific disease or type of stress, therefore the claim (and claims dependent therefrom with regard to the latter) broadly encompass any disease in response to any kind of stress. The specification further broadly defines "stress" as any physical or psychological stimulus that induces a physical stress response (see p. 4, lines 29-32).

It is noted that although the specification is silent with regard to coronary heart disease (CHD), smoking, and the serotonin long allele, the art (Arinami et al; Thrombosis Haemostasis, vol. 81, pp 853-856, June 1999) is enabling for a method of screening human subjects for increased risk of CHD in response to smoking by detecting the presence of at least one serotonin transporter gene promoter long allele.

Presence and Absence of Working Examples

The specification has no working examples, whatsoever, of any studies or methods that associated the presence of any disease in general, or of the claimed diseases, in human subjects with at least one long allele of the serotonin transporter gene promoter, either in combination or not with response to stress.

Amount of Direction and Guidance

The specification asserts that the method of the invention comprises determining the presence of at least one, and preferably two serotonin transporter gene promoter long alleles in a subject and that the presence of at least one and particularly two long alleles indicates the subject is at increased risk of disease as compared to a subject with no long alleles or with only one long allele (page 2). The specification teaches analyzing human subjects, not including those with medical or psychiatric disorders or current medication use, for 5HIAA levels (primary serotonin metabolite) in response to tryptophan depletion and response to the antagonist pindolol. The specification further analyzes differences in biological responses to tryptophan depletion or infusion, such as heart rate, mean arterial pressure, epinephrine and norepinephrine levels, cortisol levels, and prolactin levels in subjects with either short or long serotonin transporter gene promoter polymorphisms. The specification, however, does not provide any examples of an association between the presence of any of the claimed diseases and subjects with the long allele serotonin transporter gene polymorphism. Thus, while the study provided in the specification illustrates that subjects with different serotonin transporter gene promoter alleles have different biological responses to tryptophan infusion or depletion, the specification does not analyze the association between the presence of any of the claimed diseases and the long allele of the serotonin transporter gene promoter in subjects either in the presence or absence of a response to stress. It would essentially be an unpredictable trial and error process to determine whether subjects with the long allele of the serotonin transporter gene promoter polymorphisms were in fact at an increased risk for developing any of either the broadly claimed category of

diseases (ie: cardiovascular diseases, autoimmune diseases, infectious diseases, gastrointestinal diseases) or specific infectious diseases (ie: influenza, tuberculosis), in response to stress, or not.

Level of predictability and unpredictability in the art

The art teaches that an association between the serotonin transport gene promoter alleles and different diseases is unpredictable. For example, Persico (Persico et al; American Journal of Medical Genetics, vol. 96, pp 123-127, 2000) teach that family based studies provide conflicting evidence of linkage or association between either the short or the long allele of the serotonin transporter gene promoter in subjects with autistic disorder (see abstract) despite the fact that elevated serotonin blood levels have been consistently found in approximately 30-50% of autistic patients (see p. 123, col. 1, 2nd para). Further, Kunugi (Kunugi et al; American Journal of Medical Genetics, vol. 96, pp 307-309, 2000) teach that while two independent research groups consistently reported a significant association between the serotonin transporter gene promoter short allele and late onset sporadic Alzheimer's disease, Kunugi could not find an association between such an allele and either early or late onset Alzheimer's disease in a Japanese population.

Further, the post filing date art demonstrates the unpredictability of the claimed methods. For example, Kendler (Kendler et al; Arch. Gen. Psychiatry, vol. 62, May 2005, pages 529-535) teaches a study which analyzed the association between serotonin transporter promoter short and long alleles, stressful life events, and depression. In contrast to the instant specification's assertions, Kendler teaches that individuals with two short alleles had an association between low threat event stress and depression. Yeo (Yeo et al; Gut, 2004, vol 53, pages 1452-1458)

teaches a study which analyzed the association between serotonin transporter promoter short and long alleles and Irritable Bowel Syndrome (a gastrointestinal disease), and found that there was an association between patients with diarrhea predominant IBS and *both short alleles*, but that no other alleles were associated with disease, in contrast to the specification's asserted association.

Additionally, applicants own post filing date art (Williams et al; Neuropsychopharmacology, 2003, vol. 28, pages 533-541) teaches an analysis of CNS serotonergic function and serotonin related gene polymorphisms, including serotonin transporter promoter short and long alleles, and teaches that the effects of serotonin related gene polymorphisms on CNS serotonergic function vary as a function of both ethnicity and gender. Williams specifically teaches that "Further research will be required to determine the mechanisms underlying these differential effects. In the meanwhile, both ethnicity and gender should be taken into account in research evaluating effects of these and related polymorphisms on CNS serotonergic function, as well as the broad range of biological and behavioral functions that are regulated by CNS serotonergic function." (see abstract). The instant specification, however, provides no assessment as to ethnicity or gender with regard to the data presented.

Thus the art not only fails to support the efficacy of the invention, but in fact, supports the unpredictability of associating serotonin transport gene promoter alleles and different diseases (even diseases which were previously found to be associated with one of the alleles), stress, and CNS serotonergic function.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of Experimentation necessary

The quantity of experimentation in this area is extremely large since the claims are broadly drawn to broad categories of diseases and any type of stress and the specification does not support the scope of the broadly claimed invention. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher*, F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the unpredictability in the art. Furthermore, the Court in *Genetech Inc. V Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

To be able to practice the invention as broadly as it is claimed, that is to determine that a subject is at an increased risk for any disease in response to stress, at an increased risk for any of the claimed diseases in response to stress, or at an increased risk for any infectious disease or any of the claimed infectious diseases, merely based on the presence of at least one long allele of the serotonin transporter gene promoter, the skilled artisan would have to perform a large number of studies, that included a sufficient number of subjects suffering from different types of cardiovascular diseases, cancers, autoimmune diseases, gastrointestinal diseases, infectious diseases, as well as a sufficient number of control subjects, in the presence of and absence of different types of stress, to determine if in fact, a subject could be determined to be at an

increased risk for developing any type of disease, in response to stress or not, or the diseases claimed, based on that subject having at least one long allele of the serotonin transporter gene promoter polymorphism.

Given the lack of guidance from the specification and the unpredictability taught in the art, such a study would be replete with trial and error analysis, the results of which are unpredictable. There is no teaching in either the specification or the art that the long allele of the serotonin transporter gene promoter is associated with *any* cardiovascular disease, such as vascular diseases, hypertension, hypotension, or aneurysms, or gastrointestinal diseases, infectious diseases, delayed wound healing, cancers, or autoimmune diseases. These diseases each represent a large category of different disorders and diseases, wherein in many cases, each disease in the large category are involved with different biological mechanisms and genes and are associated with different risk factors and response to therapies. The specification merely provides an invitation for further experimentation and the claims are broadly drawn to methods that basically represent a research project, such research project requiring extensive trial and error analysis and which results are unknown and unpredictable, as illustrated by the state of the art at the time of filing.

Conclusion:

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is

the position of the examiner that it would require undue experimentation for one of skill in the art to make or use the methods of the claims as broadly written.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Arinami et al., (Thrombosis Haemostasis, vol. 81, pp 853-856, June 1999) as defined by Grassi et al (Circulation, vol 90, pp 248-253, 1994).

The claims are drawn to a method of screening human subjects for increased risk of disease, wherein the disease is cardiovascular disease (claim 2), by determining the presence of at least one serotonin transporter long allele in a subject wherein the presence of at least one long allele serotonin transporter gene promoter genotype indicates that said subject is at increased risk of disease in response to stress. Arinami teaches of analyzing patients with coronary artery disease for a serotonin transporter gene promoter polymorphism (see abstract, pp 853-854). Arinami teaches that the L allele (the long allele) was observed more frequently in patients with coronary heart disease ($p < 0.03$) and that this association was stronger ($p<0.003$) in patients that also smoked. The specification defines stress as any physical or psychological stimulus that induces a physiological stress response in a subject (e.g. increased heart rate, increased blood pressure...). As defined by Grassi et al (abstract, col. 1, lines 18-22) smoking markedly and

significantly increased mean arterial pressure, heart rate, calf vascular resistance, and plasma norepinephrine and epinephrine levels.

The teachings of Arinami teach a study which analyzed (screened) for an association between coronary heart disease (cardiovascular disease) and the long allele of the serotonin transport gene promoter in patients who smoked, and therefore, the teachings of Arinami anticipate the instantly claimed invention.

Conclusion

7. No claims are allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton
Primary Examiner
Art Unit 1634
11/3/05